

## EDITORIAL COMMENT

## Apolipoprotein A-I Therapy

## Promise, Challenges, and Disappointment\*

Michael H. Davidson, MD

*Chicago, Illinois*

Since 1988, with the release of the National Cholesterol Education Panel (NCEP) Adult Treatment Panel I, low-density lipoprotein cholesterol (LDL-C) has been the primary focus of therapy (1). Although the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio is a better cardiovascular risk predictor (2), the consensus at the time was that the clinical evidence only supported LDL-C reduction to improve outcomes. For the past 20 years, targeting LDL-C has yielded impressive results, especially with statins, yet low HDL-C continues to predict increased cardiovascular events, even in conjunction with low LDL-C levels (3). High LDL-C and low HDL-C are approximately equal risk factors in population studies, and both lipoproteins are causally linked to atherosclerosis (4). Severe apolipoprotein (apo) A-I deficiency (familial hypoalphalipoproteinemia) is associated with very premature coronary heart disease similar to heterozygous familial hypercholesterolemia (5). However, unlike LDL metabolism, in which the cellular regulation is well understood, HDL and the process of reverse cholesterol transport remain complex and elusive targets of drug development (6).

**See page 1111**

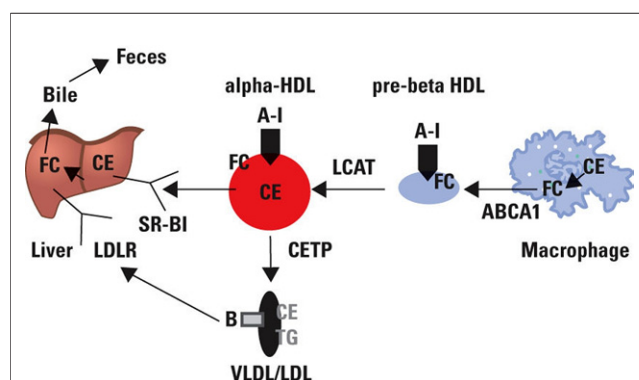
The process of reverse cholesterol transport involves the efflux of free cholesterol in the macrophage to discoidal pre- $\beta$ 1-HDL. Discoidal pre- $\beta$ 1-HDL is formed by apoA-I synthesized in the liver and intestine with the addition of phospholipid. These delipidated HDL particles pick up free cholesterol from cell membranes through the

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Department of Preventive Cardiology, University of Chicago Pritzker School of Medicine, Chicago, Illinois. Dr. Davidson is on the Speakers' Bureau for Abbott, AstraZeneca, GlaxoSmithKline, and Merck; on the advisory board/consultant for Abbott, Aegerion, Amgen, AstraZeneca, Atherotech, Daiichi-Sankyo, DTC MD, Esperion, GlaxoSmithKline, iMD (Intelligent Medical Decisions), Kinemed, LipoScience, Merck, NovoNordisk, Roche, sanofi-aventis, Synarc, Takeda, and Vindico Medical Education; has received grant/research support from Abbott, AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Merck, and Roche; and is on the Board of Directors for DTC MD, Omthera, Professional Evaluation Inc. Medical Education Company, and Sonogene.

adenosine triphosphate-binding cassette-A1 (ABCA1) transporter to become discoidal  $\alpha 4$ -HDL. As this particle matures, it accumulates more free cholesterol from the cells (including macrophages) through the ABCG1 transporter. The free cholesterol is converted to cholesteryl ester by lecithin cholesterol acyltransferase, which adds a fatty acid from phosphatidylcholine to free cholesterol, to form spherical  $\alpha 3$ -HDL. Through the action of lipoprotein lipase on triglyceride-rich lipoprotein, surface apolipoproteins are transferred to HDL by cholesteryl ester transfer protein (CETP), and triglyceride is transferred to HDL in exchange for cholesteryl ester to form  $\alpha 2$ -HDL, which is further enlarged to  $\alpha 1$ -HDL. Elevated  $\alpha 1$ -HDL or large HDL particles are more likely associated with reduced cardiovascular disease compared with other HDL lipoprotein subfractions. Therefore, therapeutic approaches that increase  $\alpha$ HDL may result in a greater cardiovascular benefit. The  $\alpha 1$ - and  $\alpha 2$ -HDL donates cholesteryl ester to the liver through the scavenger receptor B1. Once in the liver, cholesteryl ester is used for bile formation and secreted into the intestine. A potential marker of enhanced reverse cholesterol transport is an increase in fecal cholesterol (Fig. 1).

In animal models, increasing apoA transgenically or infusing recombinant HDL promotes prominent regression of atherosclerosis and enhanced macrophage-specific reverse cholesterol transport. On the basis of these animal models, this approach appears to offer the greatest clinical potential for HDL-based therapies (7). There are also 3 intriguing small human trials demonstrating that different approaches to increasing lipid-poor apoA-I acceptors induce regression of atherosclerosis in only 6 weeks in humans.



### Figure 1 The Process of Reverse Cholesterol Transport

Discoidal pre- $\beta$ -high-density lipoprotein (HDL) is converted to spherical  $\alpha$ -HDL as cholesterol ester (CE) accumulates and is returned to the liver by scavenger receptor B1 (SR-B1) or transfers the cholesteryl ester to apolipoprotein B lipoproteins by the cholesteryl ester transfer protein (CETP). ABCA1 = adenosine triphosphate-binding cassette-A1; A-I = apolipoprotein A-I; B = apolipoprotein B; FC = free cholesterol; LCAT = lecithin cholesterol acyltransferase; LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor; TG = triglycerides; VLDL = very low-density lipoprotein.

Three small intravascular ultrasonography trials with either apoA-I Milano, recombinant HDL, or delipidated HDL infusion showed a similar 3.5% to 5% decrease in atheroma volume compared with baseline, but owing to the small sample sizes, these decreases were not statistically significantly different from placebo (8–10).

An oral drug, RVX-208, selectively induces nuclear transporter factors that increase hepatic and intestinal production of apoA-I. In monkeys, this compound significantly increased HDL-C by >40%, and the serum of treated animals was shown to enhance cholesterol efflux from foam cells (11). A small and short-term human trial demonstrated significant increases in total plasma apoA-I, but most of the increase was in pre- $\beta$ -HDL (11). This was the first oral small molecule that stimulates apoA-I production to enter phase II trials.

Unfortunately, the early promise of significant increase in apoA-I levels in the monkeys was not replicated in this phase II trial (12). There were only modest increases in HDL-C and apoA-I (8.3% and 5.6%, respectively) at the highest dose of RVX-208, which was also associated with an unacceptable 10% rate of transaminase elevation (3 times upper limit of normal). A potentially encouraging signal was an approximately 20% increase in large HDL particles, which suggests an improvement in reverse cholesterol transport due to enhanced maturation to more lipid-rich HDL. These modest changes in large HDL particles with RVX-208 is less than can be achieved with niacin therapy (13).

Based on the disappointing efficacy of RVX-208, safety issues due to transaminase elevations, and significant regulatory hurdles, major challenges lie ahead for the future clinical development of this nuclear transcription factor for increasing apoA levels. Hopefully, therapeutic approaches to modulating apoA-I production will continue to progress because the potential clinical benefits represent a major unmet need in the treatment and prevention of cardiovascular disease. The recent data regarding anacetrapib, a CETP inhibitor in the DEFINE (Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib) trial (14), while encouraging, is a very different approach to affecting HDL metabolism, than enhancing apoA-I production. Decreasing HDL catabolism through CETP inhibition may not affect reverse cholesterol transport to nearly the same magnitude as a potent stimulator of apoA-I production. The promise of apoA-I therapy remains unfulfilled, and owing to the complex nature of HDL metabolism and a difficult regulatory pathway, there is an uncertain future for one of the most highly sought targets for the prevention and treatment of atherosclerosis.

**Reprint requests and correspondence:** Dr. Michael H. Davidson, Preventive Cardiology, University of Chicago Pritzker School of Medicine, 515 North State Street, Suite 2700, Chicago, Illinois 60654-4854. E-mail: [michaeldavidson@radiantresearch.com](mailto:michaeldavidson@radiantresearch.com).

## REFERENCES

1. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med* 1988;148:36–69.
2. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screeners of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823–8.
3. Cholesterol Treatment Trialists' CTT Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–81.
4. Gordon DJ, Knoke J, Probstfelt JL, et al. High density lipoprotein cholesterol and coronary heart disease in hypercholesterolemic men. The Lipid Research Clinics Coronary Primary Prevention Trial. *Circulation* 1986;74:1217–25.
5. Schaefer EJ, Santos RD, Asztalos BF. Marked HDL deficiency and premature coronary heart disease. *Curr Opin Lipidol* 2010;21:289–97.
6. Duffy D, Rader DJ. Update on strategies to increase HDL quantity and function. *Nat Rev Cardiol* 2009;6:455–63.
7. Tangirala RK, Tsukamoto K, Chun SH, Usher D, Puré E, Rader DJ. Regression of atherosclerosis induced by liver-directed gene transfer of apolipoprotein A-I in mice. *Circulation* 1999;100:1816–22.
8. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:2292–300.
9. Tardif JC, Grégoire J, L'Allier PL, et al., for the Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) Investigators. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. *JAMA* 2007;297:1675–82.
10. Waksman R, Torguson R, Kent KM, et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. *J Am Coll Cardiol* 2010;55:2727–35.
11. Bailey D, Jahagirdar R, Gordon A, et al. RVX-208: a small molecule that increases apolipoprotein A-I and high-density lipoprotein cholesterol in vitro and in vivo (erratum in: *J Am Coll Cardiol* 2010;56:825). *J Am Coll Cardiol* 2010;55:2580–9.
12. Nicholls SJ, Gordon A, Johansson J, et al. Efficacy and safety of a novel oral inducer of apolipoprotein A-I synthesis in statin-treated patients with stable coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 2011;57:1111–9.
13. Kuvlin JT, Dave DM, Sliney KA, et al. Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. *Am J Cardiol* 2006;98:743–5.
14. Cannon CP, Shah S, Dansky HM, et al., for the DEFINE Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010 Nov 17 [E-pub ahead of print].

**Key Words:** apoA-I ■ drug therapy ■ HDL.